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Head-to-head comparison of ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC PET/CT: a prospective study of 59 patients with neuroendocrine tumors.

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Short title: ^{64}Cu-DOTATATE vs. ^{68}Ga-DOTATOC for NETs

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ABSTRACT

Somatostatin receptor imaging is a valuable tool in the diagnosis, follow-up and treatment planning of neuroendocrine tumor (NET) patients. Positron emission tomography (PET) based tracers using ^{68}Ga as the radioisotope have in most centers replaced single-photon emission tomography (SPECT) based tracers as the gold standard. ^{64}Cu-DOTATATE is a new PET tracer that has been shown to be far superior compared to the SPECT tracer ^{111}In-DTPA-octreotide. Due to advantages of ^{64}Cu compared to ^{68}Ga, we hypothesize that the tracer could have a higher sensitivity than ^{68}Ga-based tracers. To test this hypothesis, we compared on a head-to-head basis the diagnostic performance of ^{64}Cu-DOTATATE with that of ^{68}Ga -DOTATOC in NET patients. **Methods:** Fifty-nine NET patients were scanned both with ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC PET and computed tomography (CT) and compared on a head-to-head basis. Discordant lesions were verified during at least 30 months of follow-up. **Results:** A total of 701 lesions were concordantly detected on both ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC PET/CT scans while an additional 68 lesions were found by only one of the scans. ^{64}Cu-DOTATATE showed 42 lesions not found on ^{68}Ga-DOTATOC of which 33 were found to be true positive on follow up. ^{68}Ga-DOTATOC showed 26 lesions not found on ^{64}Cu-DOTATATE of which 7 were found to be true positive on follow up. False positives were mainly lymph node lesions. Accordingly, 83% of the additional true lesions only found on one of the scans were found by ^{64}Cu-DOTATATE. On a patient-basis additional true lesions were found by ^{64}Cu-DOTATATE and

^{68}Ga-DOTATOC in 13 and 3 patients, respectively. All patients with additional lesions also had concordant lesions found by both scans. **Conclusion:** ^{64}Cu-DOTATATE possesses advantages in the detection of lesions in NET patients compared to ^{68}Ga-DOTATOC. Although patient based sensitivity was the same for ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC in this cohort, significant more lesions were detected by ^{64}Cu-DOTATATE. Furthermore, the shelf life of more than 24 hours and the scan window of at least 3 hours make ^{64}Cu-DOTATATE very favorable and easy to use in the clinical setting.

INTRODUCTION

The diagnosis of neuroendocrine tumors (NETs) is a challenging process since the symptoms are highly variable and the tumors are often small, and can arise in all parts of the body.

On average there is 5-7 years delay from first symptoms to diagnosis in patients with NETs (*1*) and by then 20-50 % of the patients have developed metastatic disease (*2*). Therefore, there is a great need for an early diagnosis to reduce unnecessary delay. This may be obtained by a sensitive and easy accessible diagnostic imaging method. Furthermore, sensitive imaging modalities are crucial in the long term surveillance of neuroendocrine tumors to detect possible progression at an early stage in order to rapidly change the treatment strategy.

One common feature for most NETs is the expression of abundant somatostatin receptors on the surface of tumor cells, which makes molecular imaging with radionuclide coupled somatostatin analogues a strong diagnostic tool (*3*). Five subtypes of somatostatin receptors (sst) have been identified: sst1-sst5 (*4*). In NETs, mainly sst2 is expressed and to a lesser degree sst1 and sst5. More seldom sst3 and sst4 are found (*5-7*). Several radiotracers composed of a somatostatin analogue chelated to a radioisotope have been developed for somatostatin receptor imaging. Even small modifications of the amino acid sequences as well as the conjugation to a chelator and the choice of isotope lead to changes in the affinity towards the different somatostatin receptors (*8,9*).

Imaging of somatostatin receptors in NETs was initially achieved by gamma cameras using either planar or single-photon emission tomography (SPECT) technique and in most of North America this is still the case using ^{111}In- DTPA-octreotide.

The positron emission tomography (PET) based tracers, however, possess major advantages compared to γ-emitting tracers, both in terms of detection rates and the quantitative nature (*9-14*). The Nordic Guidelines state that PET is preferred over SPECT in the diagnostic work up for NETs and in the European Neuroendocrine Tumor Society´s consensus guidelines, this recommendation of somatostatin receptor imaging PET is supported mainly for the low-proliferative gastro-enteropancreatical tumors but also for neuroendocrine carcinomas with Ki67 below 55 % and for low grade lung NETs (*15-19*).

Many NET centers in Europe, including Copenhagen, have switched to PET based imaging of NETs using mainly ^{68}Ga as the positron-emitting radioisotope coupled to different somatostatin analogues. The three most widely used are: ^{68}Ga-DOTA-l-Nal^{3} -octreotide (^{68}Ga-DOTANOC) with binding affinity mainly for sst2, sst3 and sst5, ^{68}Ga-DOTA-Tyr^{3}-octreotide (^{68}Ga-DOTATOC) with binding affinity mainly for sst2 and sst5, and ^{68}Ga-DOTA-Tyr^{3}-octreotate (^{68}Ga-DOTATATE) that mainly binds to sst2 but with the highest affinity of all (*3*). The U.S food and drug administration, FDA, has approved ^{68}Ga-DOTATATE for diagnostic imaging of neuroendocrine tumors in June 2016.

Recently, we introduced ^{64}Cu-DOTA-Tyr^{3}-octreotate (^{64}Cu-DOTATATE) as a new PET tracer for somatostatin receptor imaging. Compared to ^{111}In-DTPA-octreotide, it was superior both in relation to radiation dose and in lesion detection rates when tested on a head-to-head basis in 112 patients (*14,20*). The lower positron range of ^{64}Cu compared to ^{68}Ga theoretically leads to a better spatial resolution, and the physical half-life of 12.7 hours makes ^{64}Cu-DOTATATE very attractive for routine use in a clinical imaging setting. In Copenhagen the currently used tracer is ^{68}Ga-DOTATOC. The aim of the present study was therefore to compare, on a head-to-head basis, ^{64}Cu-DOTATATE with one of the currently most used PET tracer for NETs, ^{68}Ga-DOTATOC. In order to determine whether discrepant lesions were true or false, clinical follow up for 2 years as a minimum was undertaken.

MATERIALS AND METHODS

Study Design and Patients

Sixty patients, of which 59 were evaluable, were prospectively enrolled in the study from the Departments of Clinical Endocrinology and Gastrointestinal Surgery in the Neuroendocrine Tumor Center of Excellence at Rigshospitalet, Copenhagen. All recruited patients were followed at the Center and the inclusion criteria were primary staging or restaging. The study was approved by the Regional Scientific Ethical Committee (H-D-2008-045) and all participating patients signed an informed consent form. From June 2012 until March 2013,

sixty patients had both a ^{68}Ga-DOTATOC PET/ computed tomography (CT) and a ^{64}Cu-DOTATATE PET/CT scan within a time span of one week. Follow-up ended august 2015 for evaluation of whether discrepant lesions found by only one of the two PET tracers was true or false positive.

Synthesis and radiolabeling of ^{64}Cu-DOTATOC and ^{68}Ga-DOTATATE.

^{64}Cu-DOTATATE was produced as previously described and approved under good manufacturing practice (*20*).

The ^{68}Ga-DOTATOC synthesis based on the acetone method was fully automated using a Modular Lab system (Eckert & Ziegler, Berlin Germany) and performed according to manufacturer instructions. Chemicals were obtained from Rotem (Leipzig, Germany). The radiochemical purity of ^{68}Ga-DOTATOC was > 95 %.

Image acquisition

200 MBq of ^{64}Cu-DOTATATE was injected intravenously and a PET/CT scan was performed after 60 minutes. For the ^{68}Ga-DOTATOC scan 150 MBq was injected iv and PET/CT images were acquired after 45 minutes. The PET/CT scans were performed on a Siemens Biograph 40 or 64 PET/CT scanner (Siemens Medical Systems, Erlangen, Germany). Precautions were made that the same scanner was used for both patient scans. The CT scan performed in connection with the ^{64}Cu-DOTATATE PET-scan was of diagnostic quality with iv contrast and the other was of low-dose (120 kV,

effective 40 mAs). Both PET/CT scans were performed within a week (1-5 days apart).

The PET was acquired in three-dimensional list mode for 3 min per bed position and patients were placed with arms above the head and scanned from forehead to mid-thigh. The PET reconstruction settings were CT based attenuation correction, resolution-recovery (point spread function, TrueX) and time-of-flight (3 iterations, 21 subsets, zoom 1.0). A 2 mm full-width-at-half-maximum Gaussian filter was then applied to all images post-reconstruction. PET slice thickness was 2mm.

Image analysis

An experienced team with a nuclear medicine specialist and a radiologist evaluated the images in consensus. In all cases, foci were identified on the PET scan and the CT was mainly used to confirm anatomical location of PET foci. All lesions on the ^{64}Cu-DOTATATE and the ^{68}Ga-DOTATOC scans were compared and discordant additional lesions were noted for each of the scans.

Lesion-sites were divided into the regions or groups: Liver, pancreas, intestines, lungs, bones, lymph-nodes, carcinomatosis and a composite called others for lesion in more seldom areas like ovaries, mamma and soft tissue. The number of PET positive lesions (up to 20) in each region were counted and maximal standard uptake values (SUV_{max}) of one concordant lesion in each region were noted. Furthermore, SUV_{max} for several reference areas (liver, bone, lung, muscle, spleen, pancreas, intestine, and pituitary) were identified in

both scans. To compute tumor-to-background ratios (TBR), background SUV values for organs (liver, lungs, pancreas, bones, and intestines) were obtained from non-diseased areas within the same organ. The fifth vertebra was used as background for bone lesions where no SUV value for reference bone in same area was available. Muscle reference was used as background in lymph nodes, and if no intestinal reference was available, also for carcinomatosis TBR. All TBR´s of corresponding ^{64}Cu-DOTATATE and ^{68}Ga -DOTATOC scans were computed from the same background area on the two scans.

Clinical follow up was more than two years. Discordant lesions were controlled by comparison to all available later images of the patients (^{68}Ga-DOTATOC PET/CT, CT and magnetic resonance (MR)) in order to verify the lesions as true or false positive lesions.

Statistical analysis

A dedicated statistical software was used for statistical analysis (IBM SPSS Statistics for Macintosh, Version 22.0, Armonk, NY: IBM Corp). For comparison of discrepant lesions using different PET tracers in the same patient, the McNemar's test for paired proportions corrected for continuity was applied. The probability that a discordant observation was found by ^{64}Cu-DOTATATE was reported with exact binomial confidence interval. The t-test for paired samples was used to compare SUV_{max} values for the two scans and for comparison of the tumor to background ratios.

RESULTS

One patient was omitted from the study at the quality check due to subcutaneously injected ^{68}Ga-DOTATOC. Characteristics of the remaining 59 patients are listed in Table 1. Comparison between the ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC PET-scans were performed at three levels (lesions, regions, and patient based). Overview of lesions and regions in patients with discordant scans are given in Table 2. Total number of all lesions and true discordant lesions are listed in Table 3.

Lesions

A total of 701 PET positive lesions were identified on both scans (concordant lesions) whereas an additional 68 lesions were found only by one of the tracers (discordant lesions).

For the 22 patients showing divergent scans, all lesions found by the two tracers are listed in Table 2 in accordance with tumor type, histology, region and follow-up. ^{64}Cu-DOTATATE found 42 discordant lesions and 33 of these were confirmed during follow-up to be true positive. A patient with a discordant bone lesion found only by ^{64}Cu-DOTATATE is seen on Figure 1. In this case, the true positive nature of the lesion was confirmed by positivity on a second ^{68}Ga-DOTATOC performed during follow up one and a half year later.

^{68}Ga-DOTATOC found 26 discordant lesions and 7 were confirmed to be true positive (Table 2). Thus ^{64}Cu-DOTATATE found significantly more true positive discordant lesions than ^{68}Ga-DOTATOC (33 additional lesions vs. 7, $P<0.001$). In 83 % of the cases a true positive discordant lesion was revealed by

^{64}Cu-DOTATATE whereas only 17% of the cases were revealed by ^{68}Ga - DOTATOC.

Regions

The additional true lesions found by ^{64}Cu-DOTATATE were located in bones, liver, lymph nodes, carcinomatosis, pancreas and soft tissue while true additional lesions were found in liver, lymph nodes and bones by ^{68}Ga-DOTATOC.

The probability that a true positive discordant lesion in bones was found by ^{64}Cu-DOTATATE was 85 %. Discordant true positive findings of carcinomatosis (n=7) were all detected by ^{64}Cu-DOTATATE.

The majority of false positive discordant foci (16 out of 19) were in both scans located in lymph nodes and to a lesser degree in bone (Table 2 and 3). There were significantly more false positive discordant findings on the ^{68}Ga-DOTATOC scan compared to the ^{64}Cu-DOTATATE scan 18 of 26 vs. 1 of 42.

Patients

The discrepant lesions between the ^{64}Cu-DOTATATE and the ^{68}Ga-DOTATOC PET-scans were found in a total of 22 patients (Table 2). Most additional lesions were found by the ^{64}Cu-DOTATATE scans (in 14 patients) while ^{68}Ga-DOTATOC showed additional lesions in 8 patients.

Follow-up confirmed that 13 of 14 patients had true positive ^{64}Cu-DOTATATE additional lesions, while a single PET-positive lymph node in the

last patient (ID 30, Table 2) could not be verified.

In 3 of the 8 patients with additional lesions found by ^{68}Ga -DOTATOC the lesions were confirmed to be true positive on follow-up. The additional lesions in the remaining 5 patients were not found in later imaging procedures (^{68}Ga-DOTATOC, CT or MR) and thus considered false positive. Altogether, significantly more patients (13 vs. 3) had additional true positive lesions found by ^{64}Cu-DOTATATE (P=0.013).

In 37 of the 59 patients, ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC scans were concordant. The two lung NETs and 26 other NETs had multiple concordant lesions. In one of the patients, concordant positive lymph nodes turned out to be false positives according to follow-up, whereas the rest were considered true positives. Nine patients showed no lesions on either of the scans and they were confirmed to be true negatives on follow-up.

Although additional true lesions were found in 13 patients using the ^{64}Cu-DOTATATE scan, and in 3 patients by the ^{68}Ga-DOTATOC scan, the sensitivity to **diagnose** NET disease in a patient was 100 % (95% CI; 93-100 %), specificity 90 % (95% CI; 56-100 %), positive predictive value 98% (95% CI; 90-100%) and negative predictive value100 % (95% CI; 66-100%) in both scans because also concordant lesions were found in all of the patients with additional lesions (Table 2). One example of such a patient is shown in Figure 2, where additional foci are shown in the intestinal region by the ^{64}Cu-DOTATATE scan. However, the diagnosis of primary intestinal tumor with wide spread metastases was the same based on either of the two scans.

Comparison of tracer uptake

^{64}Cu-DOTATATE had a significantly higher SUV_{max} compared to ^{68}Ga-DOTATOC in liver lesions, lymph nodes, pancreatic lesions, intestinal tumors and carcinomatosis lesions (Supplemental Table 1). Bones and lungs showed no significant differences. The physiological background uptake of the tracers were lower for ^{68}Ga-DOTATOC in most tissues, except in the spleen where ^{68}Ga-DOTATOC was significantly higher than ^{64}Cu-DOTATATE (Figure 3 and Supplemental Table 2).

The TBRs for the two tracers were compared within the six most typical regions: liver, lymph nodes, bone, lung, pancreas, and intestines for ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC (Table 4).

The TBR for bones was significantly higher for ^{68}Ga-DOTATOC than for ^{64}Cu-DOTATATE. All other regions showed no significant differences.

DISCUSSION

The diagnostic performance data of ^{64}Cu-DOTATATE PET compared to ^{111}In-DTPA-octreotide SPECT in NET-patients was presented recently (*14*). Twice as many lesions were found by ^{64}Cu-DOTATATE and additional organ involvement was detected in one third of the enrolled patients. No doubt that ^{64}Cu-DOTATATE should be preferred whenever possible instead of ^{111}In-DTPA-octreotide. However, most countries in Europe have changed their somatostatin receptor imaging of NET to PET technology using ^{68}Ga-based

tracers, and a similar trend applies in North America. Accordingly, the true challenge is how ^{64}Cu-DOTATATE performs in comparison with these widely used ^{68}Ga-based somatostatin receptor imaging tracers.

Both ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC were *a priori* expected to possess high sensitivities. Accordingly, it was not surprising that on a patient basis there were no differences in the diagnostics performance of the two methods.Nevertheless, significantly more additional true positive lesions were revealed by ^{64}Cu-DOTATATE compared to ^{68}Ga-DOTATOC: 33 versus 7.

It is a special characteristic of NET patients that they often live many years with widespread disease receiving multiple treatments. Changes in treatment strategy are nearly always based on clinical and/or image based signs of progression. Thus, a high performance in the detection of any new lesions is of great value in these patients. Additional lesions found by the ^{64}Cu-DOTATATE scan in the present study could not *a priori* be interpreted as sign of progression since it was the first scan with the new tracer in these patients. Thus, the clinical impact of these additional findings could not be evaluated in the present study.

It could be argued that the difference found in our study was not due to use of a different isotope but rather due to difference in the peptide. Accordingly, DOTATATE has an approximately 10-fold higher affinity (IC50) for sst2 compared to DOTATOC. Also, DOTATOC, in contrast to

DOTATATE, has some affinity toward the sst5 (*8*). However, it should be noted that sst2 receptors are expressed at a much higher level in NET than any of the other subtypes (*6*). Accordingly, differences in non-sst2 receptor affinity is not expected to be of any importance. Also the difference in sst2 receptor affinity seems not to be of clinical importance, as a recent review of PET tracers for somatostatin receptor imaging reported only marginal and no consistent differences in diagnostic performance in NET patients between the three most frequently used ^{68}Ga labelled somatostatin analogs DOTATATE, DOTATOC and DOTANOC (*3,21-27*). In the only two existing studies of head-to-head comparisons of ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC by Poeppel et al., the most lesions were seen by ^{68}Ga-DOTATOC and also the highest uptake in tumor lesion tended to be in ^{68}Ga-DOTATOC (*22,25*). In contrast to this, a meta-analysis from 2014 found a higher patient based sensitivity and specificity for ^{68}Ga-DOTATATE than for ^{68}Ga-DOTATOC (*28*). Thus no consistent conclusion exists on which peptide is the most sensitive for overall NET imaging.

The difference in lesion detection rate found by us in the current study is therefore presumed to relate to use of ^{64}Cu instead of ^{68}Ga rather than differences in peptide. If so, this is not surprising as the substantially shorter positron range of ^{64}Cu was anticipated to lead to better detection of small lesions.

The radiation burden is higher when using ^{64}Cu-DOTATATE compared to ^{68}Ga-DOTATOC mainly because of the differences in positron branching

fraction. The positron branching fraction is 0.17 for ^{64}Cu-DOTATATE and 0.89 for ^{68}Ga-DOTATOC leading to a higher dose injected needed for ^{64}Cu-DOTATATE to obtain the same number of counts as for ^{68}Ga-DOTATOC. However, the longer half-life of ^{64}Cu compared to ^{68}Ga pulls in the opposite direction. Therefor only a 33% higher dose (MBq) of ^{64}Cu-DOTATATE was used despite a nearly five times higher branching ratio for ^{68}Ga-DOTATOC. The higher radiation burden to the patient of ^{64}Cu-DOTATATE has to be taken into account. However, in our view this is not of any safety concern. A typical dose of 180-220 MBq ^{64}Cu-DOTATATE used by us, results in a radiation dose of 5.7-8.9 mSv to the patient (20) whereas 120-200 MBq of ^{68}Ga -DOTATOC results in 2.8-4.6 mSv (29). For comparison the radioactive burden from gamma-emitting tracers ^{111}In-DTPAOC or ^{111}In-DOTATOC still used at many centers is higher (5.7-11.1 and 7.0-10.0 mSv) (*30*).

The TBR, i.e. image contrast, was not significantly different for the two tracers except for bones. Presumably this is not determinant for detection of bone lesions since the mean TBRs for bone were at a high level for both scans and ^{64}Cu-DOTATATE actually did find significantly more lesions than ^{68}Ga-DOTATOC.

As a convenient standard workflow, we scanned patients after one hour post injection of ^{64}Cu-DOTATATE. This was comparable to the routine work flow for the ^{68}Ga labeled somatostatin receptor PET tracers. However, an advantage of ^{64}Cu-DOTATATE is the possibility to scan anytime between one and three hours based on the comparison of image quality and the stable SUV

values for tumors reported in our previous publication (*20*). Potential better TBRs might be found using a later scan time, but this cannot be proven in this set-up. Finally, logistically ^{64}Cu-DOTATATE is produced with a shelf-life of 24 hours circumventing the need for coordination between radiochemistry production and patient arrival.

Limitations

It cannot be ruled out that the acquisition of a diagnostic CT together with the ^{64}Cu-DOTATATE PET and not with the ^{68}Ga-DOTATOC, might have made it easier to detect small lesions using ^{64}Cu-DOTATATE. However, since the images were not blinded but pairwise, head-to-head (lesion-to-lesion), compared after the initial lesion detections, any lesions not found merely because of differences in the CT part seem unlikely. Furthermore, it is a limitation that we did not compare ^{64}Cu-DOTATATE to ^{68}Ga-DOTATATE if we wanted to assess if only the change of isotope makes a difference. High sensitivity has been seen earlier using both ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC with no clear documentations for one being superior to the other, and therefore it is most likely that it is the difference in radioisotope that made the difference in our study. Nevertheless, our main purpose was to see if ^{64}Cu-DOTATATE could compete with the commonly used ^{68}Ga-DOTATOC PET tracer.

CONCLUSION

Although patient based sensitivity was the same for ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC in this cohort, ^{64}Cu-DOTATATE had a substantially better lesion detection rate in NET patients compared to that of ^{68}Ga-DOTATOC. Follow-up revealed that the additional lesions detected by ^{64}Cu-DOTATATE mostly were true positive. The lower positron range of ^{64}Cu compared to ^{68}Ga is probably the main explanation for the better performance. Furthermore, the shelf life of more than 24 hours and a flexible scan window of at least three hours makes ^{64}Cu-DOTATATE very attractive for use in a clinical routine. Whether detection of more true lesions translates into better patient management and outcome remains to be proven.

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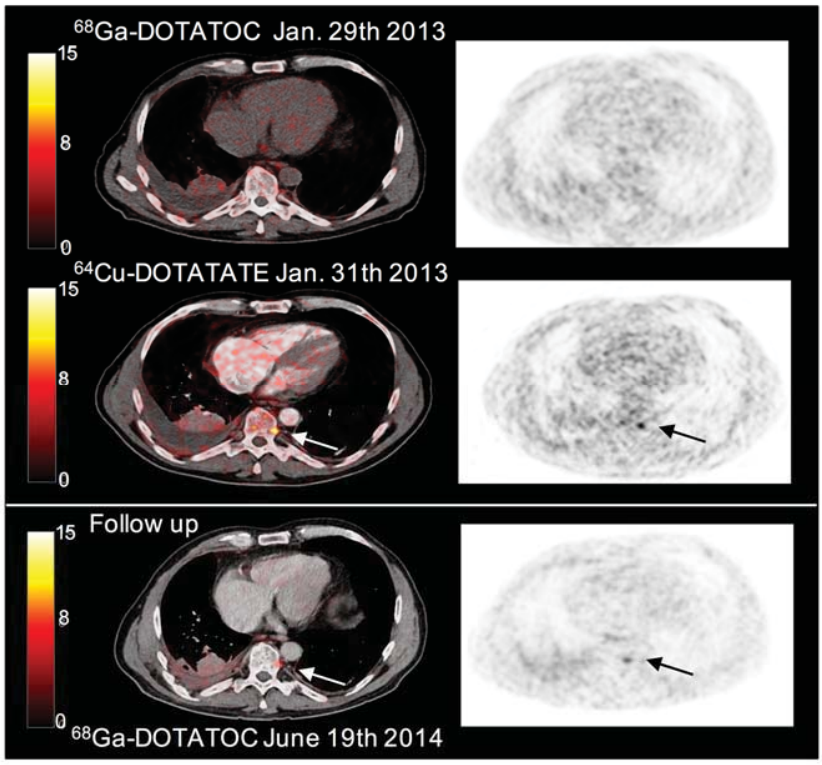

FIGURE 1.
Fused PET/CT-scans to the left and PET only to the right. An additional bone lesion was found by ^{64}Cu-DOTATATE compared to ^{68}Ga-DOTATOC (arrow). Follow-up confirmed the lesion to be true positive and visible on a later ^{68}Ga-DOTATOC scan, bottom. CT image fused with ^{64}Cu-DOTATATE is contrast enhanced.

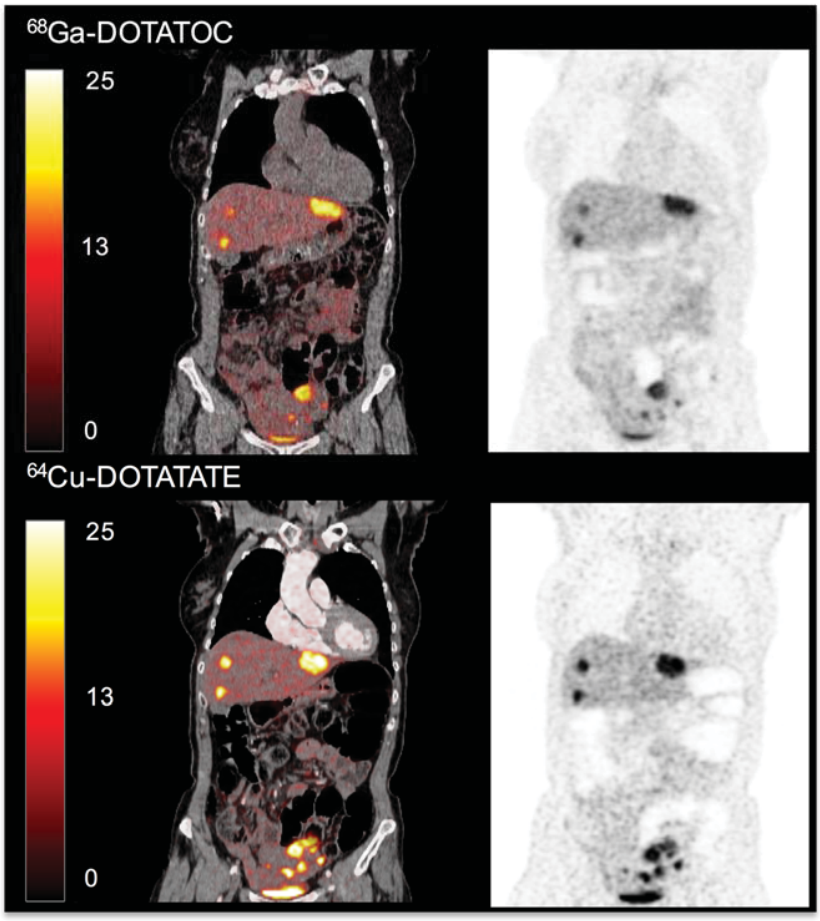

FIGURE 2.
Corresponding PET/CT (left) or PET (right) scans of a patient with intestinal NET and multiple metastases. CT image fused with ^{64}Cu-DOTATATE is contrast enhanced. Additional lesions were found in the intestinal region by ^{64}Cu-DOTATATE (lower panel) compared to ^{68}Ga-DOTATOC (upper panel).

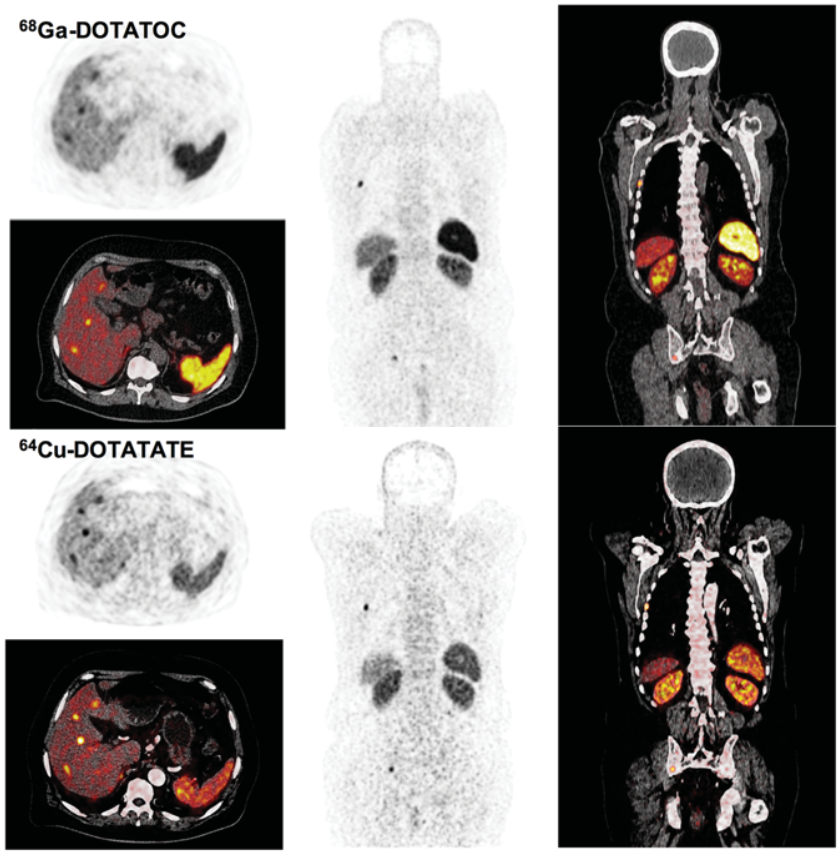

FIGURE 3.

Corresponding ^{68}Ga-DOTATOC and ^{64}Cu-DOTATATE PET/CT or PET scans of a patient with intestinal NET and multiple metastases. CT images fused with ^{64}Cu-DOTATATE are contrast enhanced. The same four liver lesions are seen on the axial images to the left and the same two bone lesions are seen on the coronal images to the right. The foci are more distinct on the ^{64}Cu-DOTATATE PET scans at the bottom compared to the ^{68}Ga-DOTATOC scans at the top. The much higher uptake of ^{68}Ga-DOTATOC in the spleen compared to ^{64}Cu-DOTATATE is also evident in this patient.

TABLE 1. Patient Characteristics n=59

Age at scanning time mean years (range)	**61 (32-81)**
Gender	
Male	35 (59%)
Female	24 (41%)
NET type	
Small intestinal	35 (59%)
Pancreatic	11 (19%)
Colonic	5 (9%)
Lung	2 (3%)
Others	3 (5%)
Unknown Origin	3 (5%)
Classification	
GEP	
G1 (Ki67 ≤2%)	12 (20%)
G2 (Ki67 3-20%)	40 (68%)
G3 (Ki67>20%)	0
Ki67 not available	5 (9%)
Lung	
TC	1 (1.5%)
AC	1 (1.5%)
Previous treatment	
Somatostatin analogs	32 (54%)
Surgery	32 (54%)
Interferon alfa	27 (46%)
PRRT	19 (30%)
Chemotherapy	16 (27%)
Radiofrequency ablation	3 (5%)
Chemoembolization	3 (5%)

NET: Neuroendocrine tumors, Ki67: Ki67 proliferation index,
PRRT: Peptide receptor radionuclide therapy

TABLE 2. Patients with discordant lesions on ^{64}Cu-DOTATATE or ^{68}Ga–DOTATOC PET.

ID	Histology		Concordant Lesions (Both scans)	Discordant Lesions		Follow-up Discordant Lesions n=68	Imaging modality at follow-up	Time until follow-up months
	Type	Ki67		Only on ^{64}Cu DOTA-TATE n=42	Only on ^{68}Ga DOTA-TOC n=26			
3	Int	4%	Lung(1), Panc(1), Int(1), LN(6)	LN(3)		TP(3)	CT	17
5	Col	13%	Int(1), LN(4)	LN(1)		TP(1)	CT	24
8	Int	5%	Int(1), LN(1)	LN(1)		TP(1)	CT	20
9	Int	2%	Bone(5)		Bone(3)	TP(2), UV(1)	Ga-PET	19
16	Int	2%	Liver (20), Carc(9), LN(8), Bone(3), Ov(2),	Carc(3), LN(3), Bone(1)		TP(1LN), UV(6)	CT	14
17	Int	4%	Liver(1) ,Int(1)		Liver(1)	TP(1)	MR	27
19	Int	3%	Int(1), LN(18)		LN(1)	FP(1)	Ga-PET	25
21	Int		Int(3), Liver(20), LN(8)		LN(12)	FP(12)	CT	26
29	Int	5%	Liver(6), LN(1)	Liver(1)		TP(1)	Ga-PET	28
30	Panc	7%	Liver(20), Panc(1), LN(4)	LN(1)		UV(1)	None	-
31	Int	2%	Lung(1), LN(19), Bone(1)		LN(1)	FP(1)	Ga-PET	22
35	Oth	15%	LN(10), Bone(15)	Bone(5)		TP(5)	Ga-PET	24
37	Int	2%	Liver(6), LN(5)	Liver(2)		TP(2)	Ga-PET	7
43	Int	3%	Int(1), Liver(10), Carc(1), LN(10), Bone(8)		Bone(2)	FP(2)	Ga-PET	6
44	Int	2%	Liver(7), LN(10)	Liver(1)		TP(1)	Ga-PET	30
45	Int	2%	Liver(3), LN(4)		LN (1)	FP(1)	CT	0
49	Panc	6%	Panc(2)	Panc(1)		TP(1)	Ga-PET	10
50	Int	10%	Int(1), Liver(20), LN(5), Bone(8),	Bone(5)		TP(5)	Ga-PET	29
51	Int	5%	Int(1), Liver(13), LN(17)		Liver(3), LN(2)	TP(4) FP(1liver)	CT	4
56	Panc	10%	Liver(1)	Liver(3)		TP(3)	MR	13
57	Int	2%	Int(1), Liver(10), LN(8), Bone(6)	LN(1), Bone(2)		TP(1bone), UV(1), FP(1LN)	Ga-PET	29
59	Int	3%	LN(1), Bone(3), Carc(3)	Carc(7), Soft(1)		TP(8)	Ga-PET/CT	10/20

Int: Small intestinal, Col: Colon, Panc: Pancreas, Oth: Other, LN: Lymph nodes, Adr.gl: Adrenal Glands, Carc: Carcinomatosis, Ov=ovaries, Soft: Soft tissue, TP:True positive, UV: Unverified/uncertain, FP: False positive, CT: High dose CT scanning, Ga-PET: ^{68}Ga-DOTATOC PET scanning with low dose CT, MR: MR scanning.

TABLE 3. Comparison of concordant and true positive discordant lesions found by concurrent ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC PET scans in 59 patients with NET.

Lesions Region	Concordant Lesions	True positive on ^{64}Cu-DOTATATE	True positive on ^{68}Ga-DOTATOC	p-value	Probability that a discordant lesion was found by ^{64}Cu-DOTATATE Estimate (95% C.I.)
Liver	298	7	3	0.34	0.70 (0.67-0.93)
LN[1]	222	6	2	0.29	0.75 (0.35; 0.98)
Bones	102	11	2	0.02	0.85 (0.55; 0.98)
Lungs	3	0	0	NA	NA
Pancreas	10	1	0	1.00	1.00 (0.05; 1.00)
Intestines	26	0	0	NA	NA
Carc[2].	25	7	0	0.02	1.00 (0.59; 1.00)
Others[3]	15	1*	0	1.00	1.00 (0.05; 1.00)
Total	701	33	7	<0.001	0.83 (0.67-0.93)

1.LN: Lymph nodes. 2. Carc=Carcinomatosis. 3.Others: Breast (10), ovary (2), adrenal gland (1), soft tissue* (3).

TABLE 4. Comparison of tumor to background ratio (TBR) for ^{64}Cu-DOTATATE and ^{68}Ga-DOTATOC in 59 patients with NET.

Region (n)	TBR ^{64}Cu-DOTATATE Mean (SEM)	TBR ^{68}Ga-DOTATOC Mean (SEM)	p-value
Liver (29)	5.49 (0.45)	4.60 (0.52)	0.13
LN (28)	17.90 (1.93)	19.99 (2.25)	0.28
Bones (17)	11.98 (2.30)	18.37 (4.11)	0.05
Lungs (3)	6.10 (1.28))	4.25 (1.41)	0.56
Pancreas (9)	9.86 (1.76))	10.34 (2.78)	0.77
Intestines (5)	4.92 (1.00))	6.48 (2.13)	0.50

(n)=number of TBR´s with available SUV values for both tumor lesion and normal corresponding tissue in both scans.
#) Paired samples test (2-tailed)

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